

Effect of transfusion therapy on intracranial stenosis in a child with sickle cell anaemia

Dear Editor,

a boy of Congolese origin, born in the UK in 2009 from sickle cell disease (SCD) carrier parents and diagnosed with homozygous SCD through new-born screening, was under annual transcranial Doppler (TCD) surveillance since the age of two at a UK district general hospital. Despite regular reviews for health monitoring in the Sickle Cell Disease clinic, optimal penicillin prophylaxis and immunisation programme, he had required multiple admissions to hospital due to frequent acute pain crises, gall stones, hepatic sequestration, ischial bone infarction, and had been started on hydroxycarbamide 29 mg/Kg/day at the age of five because of recurrent chest syndrome requiring blood transfusion. His annual TCD time-averaged maximum mean velocity (TAMMV) had been within the limits for “standard stroke risk” (<170 cm/s)¹ (Figure 1A) and he had always been asymptomatic from a neurological point of view. However, in 2018, a decrease in TCD TAMMV below 70 cm/s (67 cm/s) was noted focally in the right Middle Cerebral Artery (MCA), which progressed to 38 cm/s on close follow-up in February 2019 (Figure 1B); there were no associated neurological symptoms. Magnetic resonance angiography (MRA) confirmed right MCA stenosis, with tight stricture at the level of M1-M2, distal narrowing and beading (Figure 1C). There was no evidence of Moya-Moya disease, and contralateral vessels were normal both on TCD and MRA. There were no silent infarcts on brain imaging. He was started on monthly blood transfusions aiming to maintain HbS level below 30% of total haemoglobin,^{2,3} in addition to hydroxycarbamide; he subsequently had to be started on iron chelation treatment due to progressive increase in ferritin levels. A TCD scan repeated in June 2019, four months after starting transfusion treatment, was still abnormal, with low TAMMV of 39 cm/s, indicative of persistent right MCA stenosis. However, in September 2019, a follow-up MRA showed resolution of the previously demonstrated right MCA stenosis (Figure 1D); a TCD scan repeated in November 2019 showed significant increase in right MCA TAMMV with normalised values (94 cm/s), consistent with MRA results (Figure 1E). Transfusion treatment was continued for 18 months, before being stopped in August 2020, and hydroxycarbamide continued at a daily dose of 30mg/Kg. Last TCD follow-up in February 2021 confirmed normalised velocities, with right MCA TAMMV of 130 cm/s. No neurological or non-neurological symptoms have been recorded, and the patient is keeping well.

Albeit considered a rare disease in high-income countries, SCD is the most common severe genetic disease in the UK and France, with up to 15,000 patients in each country,¹ and is a leading cause of paediatric stroke worldwide. Children with SCD have a 410-fold increase in ischemic stroke risk as compared to their peers; stroke and silent cerebral infarcts are associated with significant cognitive impairment, lower educational attainment in childhood, worse employment status in adult life, overall reduced quality of life, and major public health expenditure, making implementation of existing primary prevention strategies crucial.¹ In the absence of prevention

programs, stroke accounts for up to 10% of deaths in SCD, with reduction of 25–30 years of life expectancy.

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) showed that by identifying neurologically asymptomatic children at high risk of stroke through TCD screening, and treating them with transfusion therapy, the risk of a first clinically overt stroke can be reduced by 90%.³ Moreover, transfusion therapy as primary prevention is associated to lower progression of silent infarcts and vasculopathy.^{3,4} Based on this evidence, clinical guidelines recommend TCD surveillance between the age of 2 and 16 to detect children at high risk of stroke.^{1-3,5} The cut-off point selected to define “high risk” (about 45% risk of stroke over 4 years) is MCA or terminal internal carotid artery (ICA) TAMMV ≥ 200 cm/s, potentially associated to severe stenosis. Velocities lower than 170 cm/s are considered to be normal, while MCA/ICA velocities between 170 and 199 cm/s are considered “conditional”, and imply tighter follow-up.^{1-3,5}

Abnormally low MCA velocities below 70 cm/sec, as in our patient, are also expression of severe stenosis and are regarded as indicative of high risk.^{1,5,6}

Few cases of MRA-proven stenoses developing in previously healthy vessels in SCD children are described in the literature. In the STOP trial, one patient in the standard care arm developed stenosis out of nine with normal MRA at baseline.⁷ Equally few cases of regression of MRA abnormality during transfusion treatment have been reported,⁸ but evidence in newly-developed stenoses is scarce. MRA is the preferred form of vascular imaging in pediatric SCD, being reliable and safe in terms of radioprotection.^{1,2,6}

In our case, a newly-developed MCA stenosis was detected during TCD surveillance and confirmed by MRA in an asymptomatic child with previously normal velocities. Interestingly, the stenosis regressed on transfusion therapy as documented by both TCD and MRA. This case therefore exemplifies how changes in TCD velocities during screening could reflect development of severe intracranial stenosis and should prompt further vascular imaging and timely treatment, thus emphasizing the importance of rigorous TCD surveillance even in children with normal TCD/MRA on previous scans. Unfortunately, organised TCD screening programmes are patchy and often not adherent to the best available evidence, possibly reflecting health disparity in this group of patients.¹

Importantly, our case also suggests that timely initiation of transfusion therapy has the potential to revert vasculopathy in neurologically intact children, with normalisation of brain vessels pathology both from an anatomic and haemodynamic point of view. The mechanism of such regression is unclear. In a previous case series⁸ showing resolution of cerebral vasculopathy in six SCD children during transfusion therapy, recurrence of arterial stenosis at the same location was observed in four of them after transfusion was discontinued. This suggests that a combination of local (endothelial

dysfunction, intimal hyperplasia) and systemic factors related to transfusion (reduced erythrocyte sickling, decreased neutrophil and reticulocyte counts, increased fetal hemoglobin) could concur to the resolution of focal stenosis. Such regression could however be treatment-dependent.

Our case is also a reminder that isolated low velocities (TAMMV <70 cm/s) in major vessels such as the MCA, can reflect high-grade stenosis, and should therefore be regarded as suggestive of high risk of stroke as well as TAMMV ≥ 200 cm/s.^{1,5}

In conclusion, this case of newly developed intracranial stenosis which resolved with prompt transfusion treatment in a boy with SCD, supports that intracranial vasculopathy in children with SCD is a dynamic process that can be reversed if recognized at an early stage and treated in a timely manner with transfusion therapy. TCD surveillance in SCD children is not only possible, but it is critical to detect new-onset abnormal velocities that should prompt further imaging and transfusion treatment. Low TAMMV (<70cm/s) as well as high (≥200cm/s) should be regarded as indicative of high risk of stroke due to severe stenosis, and should prompt further vascular imaging though MRA and appropriate treatment.

Bibliography

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Figure legend

Figure 1: Normal right Middle Cerebral Artery (MCA) Transcranial Doppler (TCD) reading during annual TCD surveillance (1A) prior to 2018; pathological right MCA TCD reading in February 2019 suggesting severe right MCA stenosis (1B); 3D magnetic resonance imaging (MRI) axial and coronal view of Time-of-Flight sequences with maximum intensity projection and multiplanar reformation reconstructions, confirming significant stenosis (arrowhead) of the proximal tract of the fronto-parietal branch of the right MCA (1C), with significant improvement after nine months of transfusion treatment (1D), consistent with improved TCD reading (1E).